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Defining acute renal dysfunction as a criterion for the severity of *Clostridium difficile* infection in patients with community-onset vs hospital-onset infection

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SUMMARY

Background—Acute renal dysfunction can be used to define severe *Clostridium difficile* infection (CDI). The Society for Healthcare Epidemiology of America (SHEA) and Infectious Disease Society of America (IDSA) guidelines define acute renal dysfunction as serum creatinine (SrCr) 1.5 times the premorbid level.

Aim—To determine the ability to assess premorbid SrCr in hospitalized patients with CDI, stratified into community-onset CDI (CO-CDI) and hospital-onset CDI (HO-CDI); and to evaluate differing definitions for premorbid SrCr as a criterion for acute renal dysfunction.

Methods—Hospitalized patients with CDI were stratified into CO-CDI and HO-CDI. The ability to assess premorbid SrCr was determined, and the incidence of acute renal dysfunction and the severity of CDI were compared using varying definitions of premorbid SrCr.

Findings—In total, 293 patients with CDI were evaluated; of these, 135 (46%) had CO-CDI and 158 (54%) had HO-CDI. Premorbid SrCr data were not available for 37 (27%) patients with CO-CDI and one (<1%) patient with HO-CDI ($P < 0.0001$). Depending on the definition of premorbid SrCr used, acute renal dysfunction ranged from 17% to 24% for patients with CO-CDI ($P = 0.26$), and from 13% to 14% for HO-CDI ($P = 0.81$). The severity of CDI could not be determined for 43 out of 293 (15%) patients, primarily due to the lack of premorbid SrCr data ($N = 38$).

Conclusion—Assessment of acute renal dysfunction and the severity of CDI was not possible for many patients with CO-CDI using the current SHEA/IDSA guidelines. Given the increasing incidence of CO-CDI, an alternative definition of acute renal dysfunction may be required.

Keywords

Healthcare-associated infections; Guideline development; Severity scoring systems; *Clostridium difficile* infection

Introduction

The Society for Healthcare Epidemiology of America (SHEA) and Infectious Disease Society of America (IDSA) 2010 clinical practice guidelines recommend the treatment of *Clostridium difficile* infection (CDI) based on severity. Two clinical parameters used to define severity are leucocytosis and an increase in serum creatinine (SrCr) level (acute renal dysfunction). A severe initial episode of CDI is defined as white blood cell (WBC) count $\geq 15,000$ cells/ μ L or SrCr ≥ 1.5 times the premorbid level.¹ The guidelines do not define premorbid SrCr. Premorbid SrCr can fluctuate during hospitalization, and categorizing patients with severe hospital-onset CDI (HO-CDI) could change based on the choice of baseline SrCr. In addition, increased incidence of community-onset CDI (CO-CDI) has been noted.² For many patients without previous exposure to a healthcare setting, it may be difficult to determine whether SrCr is ≥ 1.5 times the premorbid level due to lack of baseline or premorbid SrCr data. The purpose of this study was to evaluate SrCr as a criterion for the severity of CDI, as recommended by the 2010 SHEA/IDSA guidelines, at a tertiary care hospital. The specific aims were to determine the ability to assess premorbid SrCr in hospitalized patients with CDI, stratified into CO-CDI and HO-CDI groups, and to evaluate differing definitions for premorbid SrCr as a criterion for acute renal dysfunction.

Methods

This was a retrospective analysis of data obtained from a prospective, observational cohort study of hospitalized patients with CDI from 2006 to 2010 at a large university-affiliated, tertiary care hospital. The methodology has been described previously.³ Briefly, hospitalized patients with a positive *C. difficile* cell cytotoxin neutralization toxin B assay⁴ and diarrhoea (defined as three or more loose stools in a 24-h period) were evaluated and followed during their hospitalization and via telephone follow-up after hospital discharge for a total of three months. All patients gave their informed consent. Clinical information was collected at the time of enrolment and during the subsequent follow-up period. The diagnosis of CDI and treatment selection was made by each patient's primary medical team. The secondary analysis reported in the present paper evaluated adult patients with their first documented episode of CDI. Data collected included patient demographics (age and gender), hospital admission date, collection date of positive *C. difficile* toxin B assay, SrCr, and WBC count obtained within 24 h of the positive *C. difficile* toxin assay. Pre-admission baseline SrCr was obtained from the patient's medical chart or from the online medical record from previous hospitalizations or medical visits within the healthcare system. For baseline SrCr assessments, a trend in SrCr over the course of the hospital stay was assessed, and the chart was reviewed to determine any other obvious factor for elevated SrCr (e.g. acute renal failure during a previous admission). In these instances, baseline SrCr during a period of wellness was chosen. The study was approved by the institutional review boards of the university and the hospital (St Luke's Episcopal Hospital and University of Houston).

Stratification and definitions

Patients with CDI were stratified into CO-CDI or HO-CDI groups using the definitions suggested by the SHEA/CDC guidelines.⁵ CO-CDI was defined as positive *C. difficile* toxin assay within two days of hospital admission, and HO-CDI was defined as positive *C. difficile* toxin assay after two days of hospital admission. Direct transfer of a patient from another healthcare institution was categorized as HO-CDI. To define premorbid SrCr for patients with CO-CDI, the most recent and the oldest SrCr values measured within one year prior to the current hospitalization were collected. SrCr on the day of hospital admission and 7–10 days prior to CDI diagnosis were used as premorbid SrCr values for patients with HO-CDI. The day of CDI diagnosis was defined as the first day that a *C. difficile* toxin B

diarrhoeal stool sample was collected from the patient. Changes in premorbid SrCr over time were compared if both premorbid SrCr values were available. Acute renal dysfunction, defined as SrCr ≥ 1.5 times the premorbid level, was calculated for each patient with SrCr data for the day of CDI diagnosis and at least one premorbid SrCr value. The severity of CDI was calculated for each evaluable patient according to the SHEA/IDSA 2010 guidelines.

Statistical analysis

The ability to assess premorbid SrCr and the severity of CDI in patients with CO-CDI and HO-CDI was compared. In evaluable patients, categorization of patients with acute renal dysfunction and the severity of CDI were assessed in patients with CO-CDI and HO-CDI based on choice of baseline SrCr. STATA/IC Version 11 (StataCorp LP, Texas, USA) was used for all analyses. Categorical data were compared using Chi-squared test or Fisher's exact test, where applicable. All tests were two-tailed, and a P -value <0.05 was considered to indicate statistical significance.

Results

CDI cohort and premorbid SrCr

Two hundred and ninety-three patients with an initial episode of CDI were evaluated; of these, 135 (46%) had CO-CDI and 158 (54%) had HO-CDI. Baseline characteristics of the patients with CO-CDI and HO-CDI are described in Table I. Among the 135 patients with CO-CDI, the most recent and oldest SrCr values measured within one year prior to hospital admission were available for 87 patients (64%), and any premorbid SrCr value was available for 98 patients (73%). No premorbid SrCr data were available for the remaining 37 patients (27%). Out of 87 patients with CO-CDI who had two premorbid SrCr values, four patients had no change in SrCr, 53 patients had a decline in SrCr (range 0.05–4.2 mg/dL) and 30 patients had an increase in SrCr (range 0.07–6.1 mg/dL).

Among the 158 patients with HO-CDI, 157 (99%) had SrCr data for the day of hospital admission. Seventy-six patients (48%) had SrCr data for both the day of hospital admission and 7–10 days prior to the day of CDI diagnosis. No premorbid SrCr data were available for one patient (1%) with HO-CDI. Out of 76 patients with HO-CDI with both premorbid SrCr values, five patients had no change in SrCr, 37 patients had a decline in SrCr (range 3.4–0.01 mg/dL), and 34 patients had an increase in SrCr (range 0.05 to 1.62 mg/dL).

Change in SrCr from premorbid level to day of CDI diagnosis

Among 98 patients with CO-CDI and any premorbid SrCr data, 26 (27%) patients met the definition of acute renal dysfunction using the greatest difference in SrCr values between the available data. Among the 87 patients with CO-CDI who had two premorbid SrCr values, acute renal dysfunction ranged from 15 (17%) patients using the oldest SrCr value available to 21 (24%) patients using the most recent SrCr value ($P = 0.26$). Twenty-six patients who met the definition for acute renal dysfunction had both premorbid SrCr values available. Of these 26 patients, 10 (38%) met the definition of acute renal dysfunction using both SrCr values. Discordant results were obtained in the remaining 16 patients using the two SrCr values.

Among 155 patients with HO-CDI and SrCr values (SrCr from the day of CDI diagnosis was not available for two patients), 21 (14%) patients met the definition of acute renal dysfunction using the largest difference in SrCr values among the available values. Among the 76 patients with HO-CDI who had both premorbid values, acute renal dysfunction ranged from 11 (14%) patients using the SrCr value from the day of hospital admission to 10

(13%) patients using the SrCr value obtained 7–10 days prior to the day of CDI diagnosis ($P = 0.81$). Of these 15 patients, nine (60%) met the definition of acute renal dysfunction using both SrCr values. Discordant results were obtained in the remaining six patients using the two SrCr values.

Assessment of the severity of CDI

The severity of CDI could not be determined for 43 out of 293 patients based on the 2010 SHEA/IDSA guidelines; 38 (88%) patients were not evaluable due to a lack of any premorbid SrCr data, three patients were not evaluable due to lack of WBC data, one patient was not evaluable due to lack of SrCr data for the day of CDI diagnosis, and one patient was not evaluable due to lack of both WBC and SrCr data. In the remaining 250 patients, 67 patients had WBC count $>15,000$ cells/mm³ and were categorized as severe CDI using the SHEA/IDSA guidelines. Of the remaining 183 patients with WBC $<15,000$ cells/mm³, 161 patients had SrCr <1.5 times the premorbid level and 22 patients had SrCr ≥ 1.5 times the premorbid level. Of the 250 evaluable patients, 161 (64%) patients had mild-to-moderate CDI and 89 (36%) patients had severe CDI.

Discussion

The incidence of CDI is increasing worldwide. Many clinicians rely on the European and SHEA/IDSA CDI treatment guidelines in order to assess best practices in the treatment of CDI.⁶ Both the European and SHEA/IDSA guidelines include SrCr as one of the parameters to assess the severity of CDI. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines suggest an increase in SrCr $>50\%$ above baseline as one of the signs of severe colitis. A standardized definition of baseline SrCr is not provided in the guidelines. Other findings such as physical examination, laboratory values, colonoscopy and imaging are also used as markers of severe colitis. Severe CDI is defined as a CDI episode with one or more markers of severe colitis, including a rise in SrCr.⁷ The SHEA/IDSA 2010 clinical practice guidelines classify the severity of CDI based on two clinical parameters – leucocytosis or SrCr ≥ 1.5 times the premorbid level – for CDI treatment selection in patients with an initial episode or first recurrence.¹ Inclusion of renal dysfunction as a severity marker is appropriate given that renal dysfunction has been shown to be an independent predictor of mortality in patients with CDI.⁸ However, defining acute renal dysfunction according to the SHEA/IDSA 2010 guidelines is dependent on the availability of premorbid SrCr data, and no standardized definition of premorbid SrCr is given. In this analysis, SrCr was evaluated as a criterion for the severity of CDI based on the availability of premorbid SrCr data, as recommended by the 2010 SHEA/IDSA guidelines. Differing definitions of premorbid SrCr were used to assess the fluctuation in acute renal dysfunction rates. CO-CDI is an emerging infection and can represent up to 50% of cases seen in tertiary care hospitals.^{2,9} For this reason, results were stratified by CO-CDI and HO-CDI. The strengths of this study included the use of a large cohort of hospitalized adult patients with their first documented episode of CDI. Prospective data collection strengthened the accuracy of the results, and maximized the ability to determine whether or not the necessary parameters (WBC and SrCr) were available for assessment.

This study found that 38 of 293 (13%) patients did not have any premorbid SrCr data. Patients with HO-CDI were significantly more likely to have premorbid SrCr data than patients with CO-CDI (99% vs 73%, respectively). These results suggest that the clinical usefulness of recommendations requiring comparison with a premorbid level may be limited due to the lack of premorbid SrCr data, especially for patients with CO-CDI. Due primarily to a lack of premorbid SrCr data, the severity of CDI based on the SHEA/IDSA 2010 CDI guidelines could not be determined for 43 out of 293 (15%) patients with CDI. Other studies

have evaluated the relationship between renal dysfunction and the severity of CDI (Table II).^{10–14} One study found that a 50% increase in SrCr from baseline (defined as the lowest SrCr value within the first 24 h of hospital admission) was independently associated with CDI complications.¹⁰ This definition would not be useful in patients admitted to hospital with CDI. Pepin *et al.* used the maximum SrCr value within 24 h of CDI diagnosis to assess the severity of CDI.¹⁴ SrCr ≥ 200 $\mu\text{mol/L}$ (2.3 mg/dL) was significantly associated with CDI complications after controlling for leucocytosis and other severity parameters. Two other studies have used a SrCr >2 mg/dL to define renal dysfunction and noted an association with mortality.^{11,13} In the present study, SrCr for the day of CDI diagnosis was available for almost all patients (99%). If an absolute value for SrCr taken within 24 h of the day of CDI diagnosis was used to assess renal dysfunction, a CDI severity assessment would be possible for 98% of patients in the study population. Further research would be required to determine how to assess the severity of CDI in patients with baseline renal dysfunction or chronic renal failure if absolute SrCr on the day of CDI diagnosis was used to assess renal dysfunction. Furthermore, these studies that reported the role of acute renal dysfunction in severe CDI did not investigate its role in CDI treatment selection and subsequent impact on clinical outcomes. However, a prospective, randomized double-blind study that evaluated and validated the importance of CDI treatment selection (metronidazole vs oral vancomycin) based on the severity of CDI did not include any measures of acute renal dysfunction in CDI severity score assessment.¹⁵ More prospective studies that evaluate and validate the role of acute renal dysfunction as a severity measure in CDI treatment selection and subsequent outcomes are warranted.

In the present study, differing definitions of premorbid SrCr were used to assess the fluctuation in acute renal dysfunction rates. Discordant results for defining acute renal dysfunction were observed based on the choice of premorbid SrCr value. Although neither of the results were significant, these results illustrate the fluctuation in the severity of CDI that is determined by applying differing definitions of premorbid SrCr. A clinician would still be able to determine the severity based on their own clinical judgement. A recent study assessing renal failure and leucocytosis as predictors of CDI treatment failure reported a variation in SrCr observed from -3 to $+3$ days relative to the day of collection of the diarrhoeal stool samples.¹⁶ This study used an absolute value of SrCr >1.5 mg/dL, instead of changes from baseline, due to the lack of SrCr data prior to CDI. There seems to be a need for a standardized and practical definition of SrCr cut-off that will lead to its consistent utility in both clinical and trial settings.

This study has several limitations. Many studies have noted an association between chronic renal failure and worsening CDI outcomes.^{17–20} This finding needs to be evaluated further as patients with any type of renal impairment, including chronic renal failure, haemodialysis placement, and acute renal failure due to other factors were not excluded from this study. A renal dysfunction definition that uses SrCr at the time of CDI diagnosis will also have to account for disease severity in patients with chronic renal failure. The SHEA/IDSA guidelines state that the parameters currently recommended to define severe CDI are based on expert opinion, and there is a potential need to re-assess the currently recommended severity measures depending on the availability of future published CDI severity indexes that are validated prospectively. This analysis provides helpful data on assessing premorbid SrCr as it relates to acute renal dysfunction. Determination of CO-CDI vs HO-CDI was conducted on the day of patient enrolment, and included patient questions concerning previous hospitalizations and exposure to healthcare settings. However, patients were not further stratified by healthcare-facility-associated status in this study, as data were not available for all patients. It is possible that SrCr data from laboratories outside the healthcare system would have been available, but the likelihood that clinicians would have access to these data in a timely manner is remote. Other healthcare systems may be able to capture

more SrCr data. The *C. difficile* cell cytotoxicity neutralization toxin B assay was used in this study which, although highly sensitive and specific, is not widely used in the USA or Europe. No attempt was made to assess the clinical outcomes of patients depending on severity determinations, as the purpose of this study was to assess the effect of severity determinations using different definitions of premorbid SrCr. An analysis of other risk factors for severe CDI, such as age or other underlying comorbidities, was not performed to establish whether renal insufficiency is an independent risk factor for severe disease, or possibly indicative of another important risk factor for severe disease. Modifying the SHEA/IDSA guidelines to be able to assess renal dysfunction in the entire CDI population will require further study. Along with optimizing the definition and role of acute renal dysfunction as a marker of severity, it seems essential to evaluate various other markers and host variables in order to define severe CDI, as noted in the ESCMID guidelines.⁷ Accurate assessment of the severity of CDI is essential as severity classification is often used for treatment selection and may influence subsequent clinical outcomes.

Conclusion

Assessment of acute renal dysfunction was not possible for many patients with CO-CDI, and therefore it was not possible to determine the severity of CDI for these patients using the current SHEA/IDSA guidelines. Given the increasing incidence of CO-CDI, an alternative definition for renal dysfunction may be required. The definition of acute renal dysfunction may also need to be modified for HO-CDI in order to include patients with chronic renal failure and requiring haemodialysis who may have fluctuations in SrCr that are not clinically meaningful.

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Table I

Baseline characteristics of patients with community-onset *Clostridium difficile* infection (CO-CDI, *N* = 135) and hospital-onset *Clostridium difficile* infection (HO-CDI, *N* = 158)

Baseline characteristics	135 patients with CO-CDI <i>N</i> (%) ^a	158 patients with HO-CDI <i>N</i> (%) ^a	<i>P</i> -value
Age, years (mean ± SD)	63 ± 17	63 ± 16	NS
Gender			0.044
Male	55 (41%)	83 (53%)	
Female	80 (59%)	75 (47%)	
Race			NS
Caucasian	75 (56%)	93 (59%)	
African American	34 (25%)	38 (24%)	
Hispanic	20 (15%)	20 (13%)	
Other	2 (1%)	2 (1%)	
Unknown	4 (3%)	5 (3%)	
Past medical history			
Moderate renal disease (SrCr ≥ 2 mg/dL but not haemodialysis)	22 (16%)	35 (22%)	NS
Haemodialysis	13 (10%)	23 (15%)	NS
Diabetes	44 (33%)	60 (38%)	NS
Diabetes with end-organ failure	6 (4%)	15 (9%)	NS
Myocardial infarction	14 (10%)	27 (17%)	NS
Peripheral vascular disease	15 (11%)	13 (8%)	NS
Cerebrovascular disease	13 (10%)	15 (9%)	NS
Irritable bowel syndrome	2 (1%)	2 (1%)	NS
Crohn's disease	4 (3%)	4 (2%)	NS
Ulcerative colitis	1 (1%)	1 (1%)	NS
Diverticulitis	8 (6%)	6 (4%)	NS
Gastric ulcer disease	5 (4%)	8 (5%)	NS
Chronic diarrhoea	8 (6%)	4 (2%)	NS
Moderate or severe liver disease	13 (10%)	14 (9%)	NS
HIV/AIDS	0 (0%)	1 (1%)	NS
Severity of underlying disease (Horn's index score)			
1 (Mild)	14 (10%)	3 (2%)	0.002
2 (Moderate)	47 (35%)	41 (26%)	NS
3 (Severe)	63 (47%)	83 (53%)	NS
4 (Extremely severe)	8 (6%)	29 (18%)	0.001
Unknown	3 (2%)	2 (1%)	NS

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; SD, standard deviation; NS, not significant.

^aUnless otherwise specified.

Table II
Published studies that have assessed acute renal dysfunction as a severity measure for *Clostridium difficile* infection (CDI)

Reference	Study design	Definition		Results related to acute renal dysfunction
		Acute renal dysfunction	Outcome assessed	
Gujja and Friedenberg 2009 ¹⁰	Cross-sectional	50% increase in SrCr from baseline	Baseline SrCr	Lowest value within the first 24 h of admission
Lungulescu <i>et al.</i> 2011 ¹²	Retrospective cohort	SrCr on hospital admission >1.5 times the premorbid level	ND	Severe CDI defined as colectomy, ICU management, mortality or LOS >10 days
Pepin <i>et al.</i> 2004 ¹⁴	Retrospective chart review	SrCr 200 µmol/L (2.3 mg/dL)	NA	Complicated CDI defined as megacolon, perforation, colectomy, shock requiring vasopressor therapy, or mortality within 30 days of diagnosis
Henrich <i>et al.</i> 2009 ¹¹	Retrospective chart review	SrCr >2 mg/dL	NA	Severe CDI defined as mortality within 30 days of diagnosis, ICU admission, surgery attributed to CDI or intestinal perforation
Pant <i>et al.</i> 2010 ¹³	Retrospective chart review	SrCr >2 mg/dL	NA	Mortality
				Odds ratio (95% CI); <i>P</i> -value
				AOR = 7.13 (3.05–16.68); <0.001
				<i>P</i> -value: <0.001 ^a
				3.1 (1.8–5.2); <0.001
				2.47 (1.04–5.88); <0.05
				5.08 (1.8–13.9); 0.001

SrCr, serum creatinine; CI, confidence interval; ND, not defined; NA, not applicable; ICU, intensive care unit; LOS, length of stay; AOR, adjusted odds ratio; OR, odds ratio.

^aIn this study, SrCr on hospital admission >1.5 times the premorbid level was one of the variables included in the CDI severity index as this variable was significant on univariate analysis. Aggregated CDI severity index was evaluated for its predictability of severe CDI compared with mild-to-moderate CDI.